## Remarks

Receipt is acknowledged of the Final Office Action mailed January 29, 2003. Claims 1-10 and 19-21 are pending. Claim 19 is herewith cancelled without prejudice or disclaimer, and claim 25 is added. Therefore, with entry of this Amendment, claims 1-10, 20-21, and 25 will remain active in this case. No new matter is added with the amendments which are fully supported by the specification. Further, Applicants reserve the right to file divisional applications claiming the subject matter of the cancelled and amended claims.

Applicants note that the Examiner has made the January 29, 2003 Office Action final on the basis that Applicant's amendments necessitated the new ground(s) of rejection. Applicants traverse this assertion and request that the finality of the Office Action be withdrawn.

First, claim 19 is objected to on the basis that it depends from claim 17, which was withdrawn as directed to a non-elected invention. This new rejection was not necessitated by the amendment. The originally filed claim 19 was multiply dependent from claims 11-17. In the Office Action mailed May 1, 2002, the Examiner objected to the multiple dependency. At that time, claims 11-18 had already been withdrawn as being directed to non-elected matter. Thus, the rejection of claim 19 for depending on a withdrawn claim could have been raised in the May 1, 2002 Office Action. The Amendment to the claim, which only corrected the multiple dependencies, had no bearing on the dependency to non-elected matter.

Second, claim 19 is rejected under 35 USC §112, second paragraph, as allegedly indefinite. The Examiner asserts that claim 19 provides for the use of a mutated S. cerevisiae cell, but does not set forth any steps involved in the process, so it is unclear what process is intended to be encompassed in the claim. As the amendment of this claim only corrected multiple dependencies and did not affect the substance of the claim, this ground of rejection was available to the Examiner in the May 1, 2002 Office Action and was not necessitated by the amendment.

Third, claim 19 is rejected under 35 USC §101 for reciting a use without setting forth any steps involved in the process. For the reasons set forth above, this rejection was not necessitated by the amendment to the claim.

Fourth, claim 4 is rejected under 35 USC §112 for reciting that gpIRK1 is a human potassium channel. The Examiner notes that gpIRK1 is a potassium channel isolated from guinea pig heart muscle and this inconsistency renders the claim indefinite. The amendment to this claim only eliminated its multiple dependency upon claims 1-3. Claim 3 further limits claim 1 in that it requires the eukaryotic potassium channel to be a human potassium channel. Without addressing the merit of the rejection, the original claim 4 depended, at least partially, on claim 3, and the rejection could, therefore have been raised prior to the amendment eliminating the multiple dependency. Accordingly, this rejection was not necessitated by the amendment to the claims.

In view of the foregoing arguments, Applicants respectfully request that the Examiner withdraw the finality of the Office Action mailed on January 29, 2003.

**I. Rejections under 35 USC § 112**

Claims 4 and 19 are rejected under 35 USC § 112 as allegedly indefinite. The Examiner asserts that claim 4 recites that gpIRK1 is a human potassium channel (due to its dependency from claim 3), and that gpIRK1 is a potassium channel isolated from guinea pig heart muscle and this inconsistency renders the claim indefinite. Without acquiescing in the merits of this rejection, claim 4 has been amended to depend from claim 1, which does not require that the potassium channel be a human potassium channel. This amendment does not raise new matter because claim 4 originally depended from claims 1-3. Additionally, claim 25 has been added which depends from claim 3, reciting that the potassium channel be Kir2.1 or IRK1, which are two names for the human homolog of gpIRK1. This claim does not add new matter because Kir2.1 and IRK1 are recited in the specification as potassium channels that have been cloned (page 19, lines 18-23). Also, the specification recites that the sequence for gpIRK1, for example, may be the native sequence or one that has been modified, by mutation for example (page 4, lines 1-7 and page 5, lines 23-29). The human homolog of gpIRK1

(Kir2.1 or IRK1) differs from the guinea pig homolog in only three of 425 amino acids, *i.e.*, there is 99% homology. It would have been well within the capabilities of one of skill in the art to modify, by mutation for example, the gpIRK1 sequence to obtain the human homolog. Allowance of this claim is, therefore, requested.

Without acquiescing in the merits of the rejection of claim 19, the claim has been cancelled, thus obviating the rejection.

## II. Rejections under 35 USC § 101

Claim 19 is also rejected under 35 USC § 101 as allegedly reciting an improper definition of a process, for lack of steps. Without acquiescing in the merits of this rejection, the claim has been cancelled, thus obviating the rejection.

## III. Rejections under 35 USC § 103

Claims 1-3 and 19-21 stand rejected under 35 USC § 103 as allegedly anticipated by Gaber in view of Ketchum et al. and Fairman et al. The Examiner asserts that Gaber taught a method of identifying activators and inhibitors of heterologous potassium channel uptake transporters in mutant S.cerevisiae that had inactivated TRK1 and TRK2 channels (double knock-outs), and that Ketchum and Fairman taught that TOK1 is another potassium transport channel capable of potassium uptake, therefore it would have been obvious to combine the references and use a cell with TRK1, TRK2, and TOK1 inactivated (triple knock-outs).

Similarly, claims 1-10 and 19-21 are rejected over Gaber, Ketchum, and Fairman in further view of Tang and Rampe. The Examiner asserts that Tang teaches the desirability of expressing heart muscle potassium channels in S. cerevisiae cells which are deficient in TRK1 and TRK2 potassium channels to study the effects of the heart muscle potassium channels in these deficient cells, as taught by Gaber, Ketchum and Fairman. The Examiner asserts that Rampe teaches the desirability to study the effects of the heart muscle potassium channels in cells which have deficient endogenous potassium channels as taught by Gaber.

Applicants respectfully disagree on the basis that one of skill in the art would have been led away from the proposed combination by the teaching of Fairman. The primary purpose of the Fairman reference was to confirm the suggestions of Serrano (1991) and Bertl et al. (1998) that TOK1 channels may mediate the uptake of $K^+$ under certain conditions. See Fairman, page 155, column 1, second paragraph. Fairman demonstrated this by overexpressing the TOK1 channel in the trk1Δ trk2Δ double knock-outs, and observing that the overexpressed TOK1 rescued the double knock-outs from auxotrophic death in $K^+$-poor media. Page 154, column 2, paragraph 2. Based on these observations, Fairman explicitly teaches that if TOK1 serves as a $K^+$-uptake pathway, one of ordinary skill in the art would "expect its removal to aggregate the pathology of the trk1Δ trk2Δ double mutant." Page 153, second column, last paragraph. Fairman then confirms this hypothesis, indicating "[i]ndeed, when plated on $K^+$ limiting media, the triple knockout tok1Δ trk1Δ trk2Δ grows less well than does the double knockout trk1Δ trk2Δ (fig.5)." Thus, one of skill in the art, reading Fairman, would expect that the triple knockout, tok1Δ trk1Δ trk2Δ would be a more pathologic phenotype than the double knockout, trk1Δ trk2Δ.

The Examiner seems to acknowledge this point, noting that "the triple mutant grew poorly on potassium limiting media." Page 6, first paragraph. However, the Examiner concludes that it would have been obvious, then to use this more pathologic phenotype in the methods taught by Gaber. Applicants respectfully disagree. The more pathologic phenotype is not better complemented by the expression of heterologous proteins. As Applicants note in the specification, page 3, lines 9-12, "the study of a large number of eukaryotic potassium channels and the identification of substances which can modify the activity of the potassium channels is difficult since, for example, the human channels HERG1 or Kv1.5 cannot complement the lethal phenotype of Δtrk1 Δtrk2 on 5mM KCl. Thus no screening is possible." Given that the heterologous human potassium channels were unable to complement the double mutant, one of skill in the art would not expect those channels to be able to complement the more pathologic triple knock-out phenotype, as taught by Fairman.

What was surprisingly discovered in the claimed invention, in contrast to the teaching of Fairman, was that the triple knockout, in both liquid and solid media, was

less pathologic than the double knockout, and grew better than the double mutant. See page 29, lines 4-28. One of skill in the art reading Fairman would have never anticipated this result. It was this surprising finding that led the inventors to use the triple knockout for complementation screening. Due to this better growth, the phenotype of the triple mutant can be complemented by the heterologous expression of several $K^+$ channels, which are not able to complement the more severe phenotype of the double mutant, such as HERG and Kv1.5. See, for example, page 34, example 8 and figures 11-12.

Accordingly, one of skill in the art would not have had a motivation to combine Fairman with Gaber, but would have been led away from doing so according to the increased pathology of the triple knock-out phenotype as taught by Fairman. Applicants, therefore, respectfully request withdrawal of all rejections based upon the combination of references including Fairman.

## CONCLUSION

In view of the above amendments and remarks, applicants respectfully request that all rejections be withdrawn and the case passed to allowance. The Examiner is invited to contact the undersigned attorney for applicants at 202-912-2142 for any reason related to the advancement of this case.

Respectfully submitted,

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